

Prevalence, risk factors, and clinical correlates of ulnar artery occlusion in the general population

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Background: Occlusion of the ulnar artery is found in a substantial proportion of elderly patients. The aim of this study was to estimate the prevalence of ulnar artery occlusion in a sample of the general population of France, look for its risk factors, and evaluate its clinical correlates.

Methods: This study was an offshoot of a cross-sectional epidemiologic study in the general population of four locations in France (Tarentaise, Grenoble, Nyons, and Toulon). In phase I, random samples of 2000 individuals per location aged ≥ 18 years old were interviewed by phone for screening of Raynaud phenomenon. In phase II, subsamples of individuals were invited to a medical interview and physical examination where the presence of Raynaud phenomenon and occupational risk factors were recorded and a bilateral clinical Allen test was performed for the detection of ulnar artery occlusion. Phase II comprised 688 women and 335 men.

Results: In 36 men and seven women, at least one occluded ulnar artery was found. The estimated prevalence was 9.6% in men and 1.0% in women ($P < .001$). The occluded artery was more often in the dominant hand of both men (8.1% vs 2.4%; $P < .001$) and women (0.9% vs 0.4%; $P = .34$). Ulnar artery occlusion was found more often in men aged > 50 years (16.4%) than in younger men (1.4%; $P < .001$). Besides age, male sex, and dominant side, the only independent risk factor was an occupational exposure in men to repeated palmar trauma, with a significant quantitative relationship in the frequency of the impacts ($P < .001$) and the duration of the exposure ($P < .001$). Exposures to hand-held vibrating tools and cigarette smoking did not show a significant relationship in the multivariate analysis. Most individuals with ulnar artery occlusion did not have associated complaints; however, the diagnostic criteria for Raynaud phenomenon was validated in 13 of the 36 affected men. The association remained significant after adjusting for occupational exposure to vibrating tools. One individual reported a previous episode consistent with an attack of permanent digital ischemia.

Conclusion: This study confirms a substantial prevalence of ulnar artery occlusions in the general population, mostly in middle-aged and elderly men, which appears to be principally related to an occupational exposure to repeated occupational palmar trauma. Although there is a significant association with Raynaud phenomenon, most often the consequences of this occlusion remain subclinical. (J Vasc Surg 2009;50:1333-9.)

Eighty years ago, in 1929, Edgar Allen described his famous compression test for the evaluation of the distal arterial circulation of the upper limbs, and especially for the detection of the occlusion of the ulnar artery in patients suspected to have Buerger disease.¹ The Allen test is mainly used nowadays in the preoperative assessment of ulnar artery patency in patients undergoing coronary procedures endangering or harvesting the radial artery.²⁻⁷ It is also a

cornerstone of the clinical examination of patients with Raynaud phenomenon, in whom it is used for the etiologic diagnosis, because the evidence of an associated distal arterial disease of the upper limbs excludes a primary Raynaud diagnosis.⁸⁻¹⁰

Several studies using the Allen test in patients undergoing coronary interventions have shown a substantial prevalence of ulnar artery occlusion, most often evaluated on the nondominant hand, with a median of about 12% (range, 5.6%-27%).^{3,7,11-15} These studies were focused on the practical consequences of the demonstrated arterial occlusion and did not look for its causes, with the exception of Hosokawa et al,¹⁶ who retrospectively analyzed 2940 arms explored by the Allen test before radial catheterization, found 85 ulnar artery occlusions, and were able to find a potential explanation for only 12 patients. Thus to date, scarce information is available about the prevalence of ulnar artery occlusion, except in the coronary patient, and even more so for its etiology. We were unable to find any data from the general population about the whole issue.

In this context, an American-French study on Raynaud phenomenon,¹⁷⁻²⁰ where every examined individual underwent a bilateral Allen test as part of the systematic clinical examination, provided us with an opportunity to evaluate the prevalence of the ulnar artery occlusion in a

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Supported by National Institutes of Health grant AR-31283 from the National Institute of Arthritis and Musculoskeletal Diseases, and by the Université Joseph Fourier-Grenoble I, France.

Competition of interest: none.

Additional material for this article may be found online at www.jvascsurg.org.

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The editors and reviewers of this article have no relevant financial relationships to disclose per the JVS policy that requires reviewers to decline review of any manuscript for which they may have a competition of interest.

0741-5214/\$36.00

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doi:10.1016/j.jvs.2009.07.076

large sample of the general population of France and to look for its risk factors and clinical correlates.

METHODS

Study participants. This work was done as an offshoot of an American-French epidemiologic study of Raynaud phenomenon conducted from 1988 to 1992. The sampling procedure is detailed in previous publications¹⁷⁻²⁰ and can be briefly summarized as follows: Random samples from households of four geographic areas in the southeast of France—Tarentaise (Savoie), Grenoble (Grésivaudan), Nyons (Baronnies), and Toulon (Côte d’Azur)—were obtained from telephone lists. Every individual aged ≥ 18 years and living in the selected households was included in the survey until the planned sample size of 2000 individuals per region was reached.

In phase I, individuals were interviewed by phone about demographic and socioeconomic data and the occurrence of symptoms in the hands suggesting Raynaud phenomenon, the primary aim of the original study. This was based on two key questions:

1. Are your fingers unusually sensitive to cold? (Q)
2. Do your fingers sometimes show unusual color changes? (C)

Individuals were classified as QC+ when they answered yes to at least one question and QC– when both answers were no.

In phase II, the QC+ respondents and a random sample of QC– respondents were invited to a face-to-face interview and medical examination, where Raynaud phenomenon and other vascular acrocyanosis syndromes were diagnosed. During the same examination, potential risk factors such as cigarette smoking, alcohol consumption, occupation, and occupational exposure to vibration or hand trauma were evaluated in a standardized fashion¹⁷ as well as any history of arterial or venous diseases and other medically significant conditions.

As a result of the sampling procedure, 8040 individuals were included in phase I, with a participation rate of 80%; the proportion of QC+ was 31% in women and 20% in men. In phase II, the participation rate was 42%; owing to the selection procedure linked to the QC status, the participants were 688 women, of whom 48% were QC+, and 335 men, of whom 39% were QC+.

Vascular evaluation of the hands and Allen test. This medical interview and examination evaluated the diagnosis of Raynaud phenomenon and other vascular acrocyanosis through a standardized chart-assisted diagnostic procedure that had been previously validated.¹⁷ A thorough questionnaire about general medical history was associated, and a clinical examination included the Allen test. For subsequent analysis, the following criteria were used:

- The diagnosis of Raynaud phenomenon was settled from a previously validated procedure^{17,18} by using color charts and a scales-assisted questionnaire.

- Acrocyanosis was defined according to the medical investigator diagnosis, based on bilateral coldness, blueness, and possibly wetness of the hands at the examination.
- Palmar hyperhidrosis was defined as self-report of an excessive wetness of the hands.
- Permanent digital ischemia was determined by asking individuals about any episode of pain or discoloration of the hands. Permanent ischemia of the digits (contrasting Raynaud phenomenon and acrocyanosis) was clinically suspected in digital ulceration or necrosis, or episodes of painful coldness and blueness of one or several fingers with a duration lasting >24 hours, or both. The diagnosis was confirmed when associated with digital artery occlusions documented by imaging or functional techniques.
- The Allen test was performed on both hands, after warming them in hot water if needed, by a specially trained vascular physician (P. H. C. or C. B.). The investigator compressed both radial and ulnar arteries of the examined hand at the wrist, during which the person grasped and reopened the hand five times. After removal of the ulnar artery compression, the palm was carefully watched under a halogen illumination, looking for the velocity and homogeneity of recoloration. The test was considered positive for ulnar artery occlusion if hand recoloration was delayed by >5 seconds for the whole or part of the palm compared with a similar maneuver performed for the radial artery. In the same way, an occlusion of the radial artery was diagnosed when the recoloration of the hand was delayed by >5 seconds for the radial maneuver compared with the ulnar one. A digital artery occlusion was determined by an heterogeneity in the recoloration of the fingers detected in both maneuvers. Hyperextension of the wrist was carefully avoided during the test.

Potential risk factors and associated conditions. A number of risk factors and associated conditions were evaluated:

- Right or left dominance was determined according to the individual’s preference. Ambidextrous participants were classified as left-handed, because most of them reported they had been forced to use their right hand during childhood.
- Occupations were recorded and classified into 30 categories and subsequently classed as skilled or unskilled for the logistic regression. Retired participants were classified according to their last active occupation before retiring.
- Occupational exposure to hand-held vibrating tools was recorded and the history of exposure evaluated for each type of tool to calculate the total operating time (TOT) in hours. A diagnosis of vibration white finger was considered when the person met the criteria for Raynaud phenomenon, had been significantly exposed (TOT >1000 hours), and reported a topography of

Table I. Prevalence of arterial abnormalities detected through the clinical Allen test in 688 women and 335 men from the general population

A, Right and left hands				
Sex	Abnormal Allen test (any kind)	Artery occlusion		
		Ulnar	Digital	Radial
Women				
Right, %	1.0	0.9	0.1	0.0
Left, %	0.6	0.4	0.0	0.1
P	.44	.34	.32	.32
Men				
Right, %	8.7	6.6	1.8	0.6
Left, %	4.5	3.9	0.9	0.3
P	.03	.16	.26	.56
Women vs men				
Right hand, P	<.001	<.001	.006	.11
Left hand, P	<.001	<.001	.03	.54

B, Comparison of the dominant vs the contralateral hand				
Sex	Abnormal Allen test (any kind)	Artery occlusion		
		Ulnar	Digital	Radial
Women				
Dominant, %	1.2	0.9	0.1	0.1
Contralateral, %	0.4	0.4	0.0	0.0
P	.21	.34	.32	.32
Men				
Dominant, %	9.9	8.1	2.1	0.6
Contralateral, %	3.0	2.4	0.6	0.3
P	<.001	<.001	.02	.56
Women vs men				
Dominant, P	<.001	<.001	.002	.25
Contralateral, P	.001	.007	.11	.33

NS, Not significant.

Raynaud phenomenon consistent with the use of the tool.

- Use of the hand to hit objects during the occupation was carefully documented, with a semiquantitative evaluation of the average numbers of impacts per working day (<1, <1, and <10) for each hand and the duration of exposure in years.
- Education level was recorded on a 10-grade scale, but a two-grade classification of primary school only vs more than primary school was used in the logistic regression.
- Cigarette smoking and the use of alcoholic beverages were quantitatively evaluated through a standardized questionnaire.¹⁹ For logistic regression, they were further categorized as never smoked (<100 cigarettes) and no alcohol ever (<10 grams of alcohol per week any time).
- Participants were classified as having overt atherosclerosis when they reported a documented history of clinically patent coronary disease, cerebrovascular disease, or peripheral arterial disease.

Statistical analysis. Prevalence estimates for each location were calculated from age-standardized data to the whole

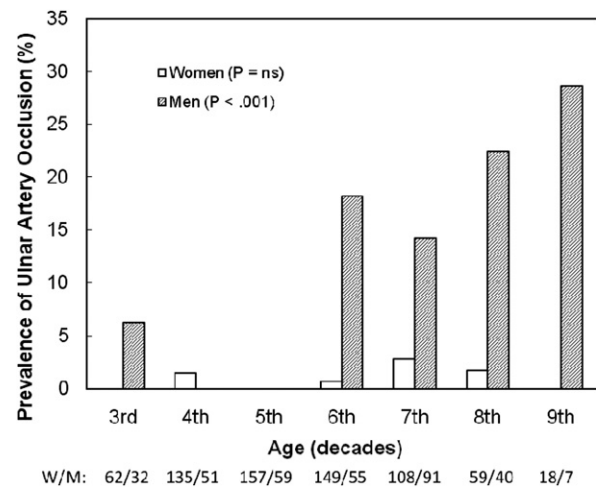


Fig 1. The prevalence of the occlusion of at least one ulnar artery as a function of age is shown in 688 women (W) and 335 men (M) from the general population.

population. Owing to the stratified sampling procedure, estimates of prevalence were computed by multiplying the proportion of the population in each QC class from phase I by the proportion of that class that had the condition examined in phase II. Adding the two resulting products gave the estimated prevalence of the condition in the whole sample.

Analyses were performed with SPSS 14 software (SPSS Inc, Chicago, Ill). The Fisher exact test for two-by-two tables or the χ^2 test was used for categoric data, with a Mantel-Haenszel test for linear association, when appropriate. The Mann-Whitney test was used for testing relationships between categoric and quantitative or ordinal variables. For multivariate evaluation of risk factors, logistic regression enforcing every factor of interest was used to ensure maximal adjustment for potentially confounding variables. A value of $P < .05$ was considered significant.

RESULTS

Results of the Allen test. Among the 1023 individuals in the general population, the Allen test of both arms showed men had a higher prevalence of the different abnormalities than the women (Table I, A and B). A difference between right and left hands is summarized in men (Table I, A), but the comparison becomes much clearer when the dominant and contralateral hands are compared (Table I, B).

Influence of sex and age on prevalence of ulnar artery occlusion. At least one occluded ulnar artery was found in 36 and seven women, which gives an estimated prevalence of 9.6% (95% confidence interval, 6.4-12.8) in men and of 1.0% (95% confidence interval, 0.3-1.7) in women ($P < .001$). The occluded ulnar artery was more often in the dominant hand of both men (8.1% vs 2.4%; $P < .001$) and women (0.9% vs 0.4%; $P = .44$).

The prevalence of ulnar artery occlusion at least in one hand, as a function of age in men and women, is illustrated in Fig 1, which shows a dramatic increase of prevalence in

Table II. Risk factors for occlusion of at least one ulnar artery in men from the general population

A, Categorical and ordinal variables (univariate statistics)			
Factor	Distribution of ulnar artery occlusion		P
	+ (n = 36), %	- (n = 299), %	
Education level			<.001
Primary school	80.6	42.5	
Secondary school	16.7	27.4	
University	2.8	30.1	
Unskilled work	71.0	53.8	.20
Occupational palmar trauma			<.001
None	28.1	78.4	
<10 years	3.1	3.0	
10-19 years	12.5	5.6	
20-29 years	12.5	5.0	
>30 years	43.8	8.0	
TOT of vibrating tools ^a			.005
<1000 h	57.6	79.9	
1000-6000 h	30.3	15.1	
>6000 h	12.1	5.0	
Cigarette smoking			.004
Never smoked	15.6	41.8	
<10 pack-years	21.9	18.1	
>10 pack-years	62.5	40.1	
No alcohol ever	8.6	12.3	.78
Overt atherosclerosis	28.1	8.0	.002

B, Quantitative variables (P from the Mann-Whitney test)

Variable	Ulnar artery occlusion, median (IQR)		P
	+ (n = 36)	- (n = 299)	
Age, y	65.0 (58.7-72.6)	52.8 (39.0-65.2)	<.001
Body height, cm	170 (166-174)	172 (168-177)	.02
Body mass index, kg/m ²	24.6 (23.4-26.6)	24.2 (22.4-26.3)	.24

C, Logistic regression (selected variables for the model were those significant in the monovariate statistics)

Predictive factor ^b	OR (95% CI)	P
Education level, primary vs higher	.58 (.28-1.21)	.14
Occupational palmar trauma; yes vs no	6.88 (4.34-10.91)	<.001
Vibrating tools, TOT ^a >1000 h	1.25 (.34-4.60)	.73
Cigarette smoking, never smoked	.54 (.22-1.37)	.19
Overt atherosclerosis	2.66 (.94-7.52)	.06
Age, OR per year	1.05 (1.03-1.07)	0.01
Height >1.75 m	.77 (.29-2.03)	.59

CI, Confidence interval; IQR, interquartile range; NS, not significant; OR, odds ratio.

^aTotal operating time (TOT) is the cumulative duration of occupational exposure to vibrating tools.

^bPrediction of having at least one occluded ulnar artery (36 of 335 men).

men starting with the sixth decade: 16.4% of men aged ≥ 50 years had at least one occluded ulnar artery compared with 1.4% of younger men ($P < .001$). By contrast, no significant change with age was found in women, the prevalence remaining <3% in any decade. Owing to the small number

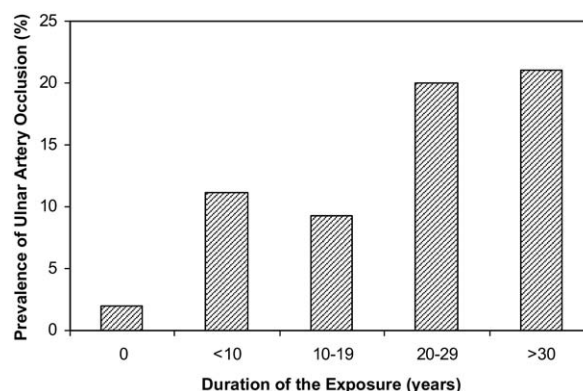


Fig 2. A, The prevalence of the occlusion of at least one ulnar artery in men is shown as a function of the duration of occupational exposure to palmar trauma ($P < .001$). **B,** Prevalence of the occlusion of at least one ulnar artery in men is shown as a function of the frequency rate of palmar trauma ($P < .001$).

of ulnar artery occlusions in women (seven), the subsequent analysis was restricted to men.

Risk factors for ulnar artery occlusion in men. To explain the strong relationship of the prevalence of ulnar artery occlusion with age in men, we looked for socioeconomic, occupational, and health-related risk factors. The results of these analyses are summarized in [Tables II, A and B](#), which give the results of the univariate analysis and show an apparently significant relationship between ulnar arterial occlusions and numerous potential risk factors, such as low education level ($P < .001$), low body height ($P = .02$), cigarette smoking ($P = .004$), overt atherosclerosis ($P = .002$), and occupational exposures to handheld vibrating tools ($P = .005$) and to repeated palmar trauma ($P < .001$).

However, because many of these variables are known to be cross-related, a logistic regression was conducted to adjust for their interactions. In this multivariate analysis, only the occupational exposure to repetitive palmar trauma remained significant in addition to age ($P < .001$), with an odd ratio of 6.88 (95% confidence interval, 4.34-10.91). This result is consistent with the lateralization of the occlusion to the dominant hand and is further illustrated by [Fig 2](#), which shows a clear quantitative relationship of the prevalence of ulnar artery occlusion with both the duration ($P < .001$) and the number of impacts per day ($P < .001$) of the occupational exposure to palmar trauma. Among the 36 men who showed an occlusion of the ulnar artery, 27 (75%) were exposed to occupational repetitive hand trauma, and this exposure was >10 years in 25 (for more details, see Appendix Table EI, online only).

Clinical correlates of occlusions of the ulnar artery in men. Among the 36 men with at least one occluded ulnar artery, only one reported a previous episode clinically consistent with a digital ischemia that had resolved with a medical treatment given by his family physician. No further diagnostic investigations had been performed, and the diagnosis remained unsettled.

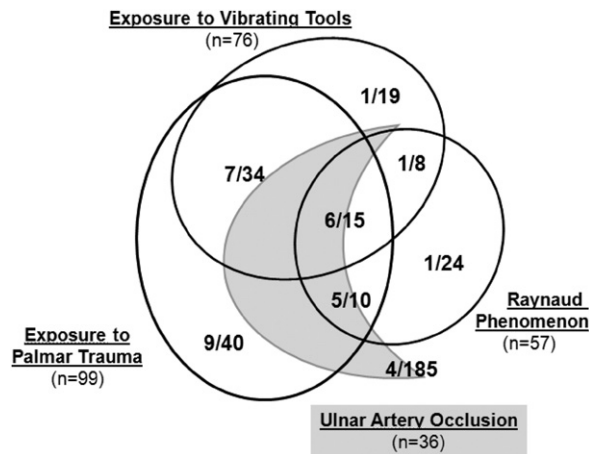


Fig 3. Venn diagram shows the association pattern of Raynaud phenomenon, exposure to vibrating tools (>1000 hours), and exposure to palmar trauma, with a projection of the ulnar artery occlusions, in 335 men from the general population. Ulnar artery occlusion appears clearly linked with the exposure to palmar trauma. Six individuals with ulnar artery occlusion met the diagnostic criteria for a Raynaud phenomenon that cannot be explained by an exposure to vibrating tools.

Of these 36 men, 13 (36.1%) met our diagnostic criteria for Raynaud phenomenon. The median age of onset was 44.5 years. Seven had had a significant exposure to vibrating tools (Fig 3), but six had none. In eight of these 13, the attacks were strictly ipsilateral ($n = 4$) or predominating ($n = 4$) on the side of the arterial occlusion. A more precise clinical description of these patients can be found in Appendix Table EI (online only).

DISCUSSION

To our knowledge, this study is the first to evaluate the prevalence of ulnar artery occlusion in the general population in France and shows that it is highly prevalent (close to 10% in men), most often found in the dominant hand of elderly men, and associated with an occupational history of repetitive palmar trauma of long duration. The occlusion of the ulnar artery was clinically silent in most participants, but 36% experienced Raynaud phenomenon, and one (<3%) reported a history consistent with an episode of permanent digital ischemia.

The reliability of these results depends on the value of the clinical Allen test, which is much debated in the cardiovascular literature for its use in the selection of patients eligible for coronary procedures using the radial artery.^{3-7,11-15} However, the sensitivity and specificity of the Allen test for the occlusion of the ulnar artery was quite high, at 95% and 100%, respectively, for Hirai et al²¹ compared with arteriography in 192 hands, and was 96% and 97%, respectively, for Pistorius et al⁸ in a series of 576 patients with Raynaud phenomenon with a plethysmographic test as reference.

The reliability of the clinical Allen test is more disputed in cardiovascular series, but here, the information asked

from the test is more about the adequacy of the ulnar collateral blood flow than the patency/occlusion pattern of the ulnar artery. Nevertheless, the specificity of the clinical Allen test remains high in these conditions, ranging from 91% to 97.1%,^{6,12,13} whereas some authors found the sensitivity was as low as 54.5%.¹³

A specificity of 91% can be too low in the context of a decision-making process when applied to the prediction of the outcome of an aggressive procedure in single patients, but it is already quite high when the information is used as an epidemiologic marker for group comparisons. The only risk associated with a lack of accuracy in this situation is a decreased power in the calculations, and indeed, the clear-cut and highly significant results we obtained in the evaluation of risk factors and clinical correlates show that our clinical marker of ulnar artery occlusion was adequate for this purpose. For the estimation of the prevalence, the reliability of the diagnostic test is more important, and because its sensitivity is debated, the figures we give could be considered as low estimates for the ulnar artery occlusions.

Furthermore, the clinical Allen test can only detect the occluded arteries, and the additional use of color duplex ultrasound exploration would certainly have detected non-occlusive lesions in addition to what we found,^{22,23} but this was not possible in the setting of field epidemiologic studies centered primarily on Raynaud phenomenon and not on arterial diseases.

We are much less confident in the reliability of the answers of the participants about their exposure to repetitive palmar trauma, which we think was probably underestimated, because some individuals may have missed recalling an usual gesture in previous work that occurred years ago and also because we did not ask for the exposure to palmar trauma during sport practice, which accounts for an appreciable number of published reports of damage to the ulnar artery.²⁴

Indeed, 27 of the 36 men with ulnar artery occlusion in this series reported a history of significant occupational exposure to repetitive palmar trauma, and 25 of these 27 were affected on their dominant hand. This epidemiologic profile clearly points toward the hypothenar hammer syndrome.²⁵ The clinical pattern is also consistent with the clinical descriptions of the hypothenar hammer syndrome. The classic clinical pattern of this condition, as it is described in case reports and in clinical series, is a permanent digital ischemia most often of acute onset, sometimes resolving spontaneously, which can also lead to digital necrosis and often requires active medical or surgical treatment.²⁵⁻²⁹

Asymmetrical Raynaud phenomenon was also reported,^{25,29,30} as well as the possibility of silent lesions of the contralateral ulnar artery.²⁸ It is not surprising that the relative frequency of these clinical pattern is quite different in the general population, with most affected individuals remaining asymptomatic, a substantial proportion complaining of Raynaud phenomenon, and very few of permanent ischemia. In a sample of 79 manual workers exposed

to repetitive palmar trauma, 14% had an occlusion of the ulnar artery or its superficial palmar branch.³¹

Although hypothenar hammer syndrome accounts for one of the first causes of permanent digital ischemia,^{29,32} this clinically prominent part of the disease is only the emerged tip of the iceberg. Indeed, the prevalence of ulnar artery occlusion in our sample of men from the general population of France is as high as 16.4% for those aged ≥ 50 years. The rich arterial supply of the hand probably accounts for a satisfactory compensation in most cases where the ulnar thrombosis is probably not associated with digital embolization. This compensation, however, may be not sufficient enough during cold exposure, because ulnar occlusion is associated with Raynaud phenomenon in our series, with an age of onset of the Raynaud phenomenon remarkably similar to what was found in the clinical series (median, 44.7 years).²⁵

The reason why some digital embolization that sometimes has clinical consequences develops in some individuals, whereas the ulnar artery in others silently occludes, is certainly a pertinent question, but we do not know the answer. The large number of asymptomatic individuals suggests, at least, to avoid treating preventively the subclinical contralateral lesions sometimes found in patients with a clinically patent hypothenar hammer syndrome.

In the men of our sample from the general population, the occlusions of the ulnar arteries are associated with many potential risk factors in monovariate statistics, including cigarette smoking, atherosclerosis, and exposure to vibrations, but only with age and occupational palmar trauma after adjusting in the logistic regression. Many elderly manual workers are smokers exposed to atherosclerosis who use vibrating tools. Our study shows that the occupational exposure to palmar trauma should not be overlooked when looking for causes of hand arterial disease in these individuals. Several studies suggest that ulnar artery occlusion of traumatic origin can be associated with pre-existing lesions of the ulnar artery.^{28,33-36} In this series, we cannot definitely rule out any contribution of atherosclerosis or vibration exposure to the lesions (they can be real but not reaching statistical significance), and the detection of rare associated diseases is beyond the scope of such an epidemiologic study in the general population such as ours. Our data, however, clearly show that repetitive palmar trauma is the main cause.

This leads to the practical aspect of avoiding missing the diagnosis of hypothenar hammer syndrome in patients with Raynaud phenomenon,³⁷ which is not easy because these patients may have an associated occupational exposure to vibrating tools.¹⁰ Typically, the clinical pattern is different, because vibration white fingers has a progressive onset, produces mild attacks usually involving mostly the non-dominant hand, and is frequently associated with pulpar hypoesthesia of the affected fingers due to its neurogenic pathogenesis. By contrast, the Raynaud phenomenon of the hypothenar hammer syndrome most often has a sudden onset, predominates on the dominant hand, and can be associated with ischemic skin lesions.³⁰ The evaluation of

an exposure to repetitive palmar trauma, whatever the occupation, should be systematic in the etiologic evaluation of Raynaud phenomenon in men, as well as the assessment of an exposure to vibrating tools and a clinical Allen test supplemented by ultrasound explorations, if any doubt remains.

CONCLUSIONS

This study demonstrates the high prevalence of the occlusions of the ulnar artery in the elderly men of the general population and their epidemiologic significance of an acquired disease, mostly related to occupational exposure to repetitive palmar trauma. By far, these occlusions do not always lead to clinical consequences. The classic pattern of digital permanent ischemia or necrosis seems relatively rare ($<3\%$); however, an association with Raynaud phenomenon was found in 36% of our participants. We propose that men with (1) exposure to occupational palmar trauma for >10 years, (2) occlusion of the ulnar artery, and (3) a predominance of Raynaud phenomenon on the side of the occlusion should be considered as having hypothenar hammer syndrome-associated Raynaud phenomenon. The possibility of a prevention of this traumatic arterial disease through information to exposed manual workers and implementation at work of procedures avoiding hand trauma should be encouraged.

The authors express their deep appreciation to Sophie Bouton and Corine Trollet for organizing the field studies.

AUTHOR CONTRIBUTIONS

Conception and design: PC
Analysis and interpretation: PC, HM
Data collection: PC, CB, MJ
Writing the article: PC
Critical revision of the article: PC, HM
Final approval of the article: PC, CB, MJ, HM
Statistical analysis: PC
Obtained funding: HM, PC
Overall responsibility: PC

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Submitted Jul 24, 2007; accepted Jul 15, 2009.

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